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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,000	02/23/2005	Yaeta Endo	3190-071	6735

33432 7590 02/02/2009

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400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

MAIL DATE	DELIVERY MODE
02/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,000	ENDO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9 and 20-29* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-7, 9, 20-24, 28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 2, 5, 6, 7, 9, and 20-29 are all the pending claims for this application.

2. Claim 21 was amended in the Response of 11/21/08.

3. Claims 25-27 are withdrawn from examination.

4. Claims 1, 2, 5-7, 9, 20-24, 28 and 29 are all the pending claims under examination.

5. This Office Action contains new grounds for rejection.

Withdrawal of Objections

Claim Objections

6. The objection to Claim 21 because the claim fails to indicate whether the antibodies for each of elements 1)-4) are in the alternative or inclusive is withdrawn. Applicants have amended the claims to insert "or" between elements 3) and 4).

Withdrawal of Rejections

Claim Rejections - 35 USC § 102

7. The rejection of Claims 5 and 6 under 35 U.S.C. 102(a) as being anticipated by Pavlinkova et al. (Peptides 24:353-362 (March 2003)) is withdrawn.

The copy of the certified translation for the Japanese language priority document, JP2002-210067 (filed 7/18/02), filed with the Response of 11/21/08 has been considered and is found persuasive in overcoming the 102(a) reference art. Applicants

have perfected their priority claim for the rejected claims pursuant to 37 CFR 1.55 and MPEP 201.13.

Claim Rejections - 35 USC § 103

8. The rejection of Claims 1, 2 and 7 under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) is withdrawn.

See the examiner's comments under section 7, which apply to Pavlinkova, and for which the rejection falls.

9. The rejection of Claims 1, 9 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) as applied to claim 1 above, and further in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07) is withdrawn.

See the examiner's comments under section 7, which apply to Pavlinkova, and for which the rejection falls.

10. The rejection of Claims 21-24 under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) is withdrawn.

See the examiner's comments under section 7, which apply to Pavlinkova, and for which the rejection falls.

11. The rejection of Claims 21 and 28 under 35 U.S.C. 103(a) as being unpatentable over Sibler et al. (J. Immunol. Methods 224: 129-140 (1999)) as evidenced by Weiss et al. (Prot. Express. Purif. 5(5):5098-517 (1994)) in view of Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) as applied to claim 1 above, and further in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07) is withdrawn.

See the examiner's comments under section 7, which apply to Pavlinkova, and for which the rejection falls.

12. The rejection of Claim 29 under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al. (Peptides 24:353-362 (March 2003); cited in the PTO 892 form of 11/26/07) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07) is withdrawn.

See the examiner's comments under section 7, which apply to Pavlinkova, and for which the rejection falls.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

13. Claims 1, 2, 5-7, 9, 20-24, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single chain antibody comprising a linker further comprising a biotin tag (the sequence of SEQ ID NO: 11), where the linker is recognizable by biotin ligase, does not reasonably provide enablement for any linker that directly crosslinks the heavy and light chain of any single chain antibody, *and* which is bound to a labeling substance, or comprises any sequence recognized by any biotin ligase, or which incorporates into its sequence any labeling substance . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims,

the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1, 2 and 7 are interpreted as being drawn to a labeled single chain antibody comprising a heavy and light chain of an antibody directly crosslinked through a linker with the linker comprising an amino acid sequence recognized by biotin ligase where the ligase binds a labeling substance to the linker and the linker is bound to the labeling substance (Claim 1), the heavy and light chains of Claim 1 are variable regions (Claim 2), and the labeling substance of Claim 1 is biotin (Claim 7), Claim 9 is interpreted as being drawn to the antibody of Claim 1 having a Kd equivalent to the parent antibody and being expressed in a cell-free wheat translation system. Claim 20 is *interpreted* as being drawn to a labeled single chain antibody comprising a heavy and light chain of an antibody directly crosslinked through a linker with the linker comprising an amino acid sequence recognized by biotin ligase where the ligase binds a labeling substance to the linker and the linker is bound to the labeling substance, where the antibody is encoded by DNA and the DNA is transcribed and translated using a cell-free wheat translation system in the presence of a labeling substance and an enzyme that catalyzes disulfide bond exchange.

Claims 21-23 are interpreted as being drawn to a method for producing an immobilized single chain antibody comprising any one of the following four antibodies 1) comprising a heavy and light chain crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase

and the ligase binds to labeling substance to the linker, 2) comprising a heavy and light chain variable regions crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker, 3) comprising a heavy and light chain crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker and the labeling substance is biotin, or 4) comprising a heavy and light chain variable regions crosslinked thru a linker and the linker is bound to a labeling substance where the linker comprises a domain recognized by a biotin ligase and the ligase binds to labeling substance to the linker and the labeling substance is biotin, and where any one of the these antibodies binds to a substance recognizing the labeling substance when brought into contact with a reaction plate being coated with the substance (Claim 21), where two or more different kinds of immobilized antibodies are immobilized on the plate (Claim 22), and the labeling substance is biotin and the substance the labeling substance reacts with is steptavidin (Claim 24). Claim 28 is interpreted as the method being drawn to an immobilized antibody produced by the method of Claim 21 having the equivalent Kd as the parent antibody where the method uses a cell-free translation system.

Claim 29 is *interpreted* as being drawn to a product-by-process claim for a labeled single chain antibody having a Kd equivalent to the parent antibody and produced a method where DNA encoding a heavy chain and a light chain against a specific antigen and a linker comprising a labeling substance being incorporated into a

part of the linker, where the expressed protein comprises the heavy and light chains being linkered by the linker, and where the DNA is subjected to transcription and translation in a wheat embryo, cell-free protein translation system in the presence of a labeling substance and an enzyme that catalyzes a disulfide bind exchange reaction.

Claims 5 and 6 are interpreted as being drawn to a single chain antibody with a linker cross-linking the heavy and light chain, where the linker comprises a labelling substance incorporated as part of the linker and where the heavy and light chains are variable regions crosslinked through the linker.

The level of skill required to generate the antibodies is that of a molecular immunologist.

Disclosure in the Specification

The specification makes a very general disclosure for a linker which can accommodate a labeling substance and all of which can be inserted between the heavy and light chain of an antibody or the VH and VL domains of a single chain antibody. The specification makes a very general disclosure for inserting a biotin tag into the linker and which would be recognized by biotin ligase. The linkers and labeling substances associated with linkers are disclosed on p. 16, lines 9-16, p. 18, lines 4-13, p. 24, lines 14-24 and in Figure 1, especially the linkers of SEQ ID NOS: 10 and 11.

In order to make any one single chain antibody that presumably works (meets the enablement requirement), the ordinary artisan would look to the specification and notice that certain requirements are taught in creating the final product:

> "As a host into which a translation template is introduced, a wheat embryo-derived cell-free protein synthesis system that can be used in normal protein synthesis and which is capable of retaining a disulfide bond of a single chain antibody is used. The reason this system is used is that an antibody produced with a different cell-free protein synthesis system is unable to sufficiently retain a tertiary structure for recognizing an antigen, and exhibits only a low Kd value (Alexander Zdanov et al;, Proc. Natl. Acad. Sci. USA, Vol 91, pp. 6423-6427(1994); C. Roger Mackenzie et al., The Journal of Biological Chemistry, Vol. 271, pp. 1527-1533 (1998))" (see pp. 26, line 16- p. 27, line 1),

and in the working example for the only biotinylated scFv antibody reduced to practice (anti Salmonella scfv; Example 1), the specification teaches using an anti-Salmonella single chain antibody where

> "Since a formation in which one disulfide bond is present respectively in the VL chain and VH chain is indispensable to synthesize a single chain antibody in an active form (Zdanov, A. L. Y., et al., Proc. Natl. Acad. Sci. USA, 91, 6423-6427 (1994)), the aforementioned single chain antibody was used as the subject of the method of this invention" (see p. 53, lines 17-23).

Thus, it seems that a critical feature of the single chain antibody is that each of the VH and VL domains should contain one amino acid residue capable of forming a disulfide bond.

Additionally, when looking to the peptide linker in the working example (Example 1), Applicants disclose the wild-type linker (SEQ ID NO:10) and the biotin tag linker of SEQ ID NO:11 as the only linker to replace the wild-type linker (figure 1). This biotinylated anti-Salmonella antibody is also shown to retain antigen specificity in Example 2(2) and Figure 3, and binding capacity for streptavidin in Example 2(3) and Figure 4.

Based on the guidance provided in the specification, the ordinary artisan would have been enabled to produce a single chain antibody comprising a sulfide residue in each of the VH and VL domains to allow disulfide bonding and a peptide linker of SEQ ID NO: 11 comprising the biotin tag. No other biotin linker peptides are disclosed. Because a linker is critical for maintaining a spatial distance between the scfv variable domains and to avoid introducing a steric hindrance in the folding of the antibody, the ordinary artisan could not predict which linkers comprising any labeling substance much less one recognized by biotin ligase, could be used to make the product invention absent undue trial and error experimentation.

The ordinary artisan in looking to Example 3 of the specification could not have reproduced the particular embodiment represented by this example. The same anti-Salmonella scfv antibody was engineered to contain a polyhistidine peptide incorporated in the linker part of the scfv. The specification does not disclose the length of this linker or its position within the wild-type linker. On p. 67 at lines 17-19 of the specification Figure 1 is referred to as providing the structure for the “scfv-pHIS-pEU” plasmid. The only version of Figure 1 filed on 1/18/05 does not contain a depiction for

the alleged "scfv-pHIS-pEU" plasmid. Thus it is not clear how the ordinary artisan could even reproduce this example of the specification absent some structural detailed information.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass any linker capable of binding to a labeling substance or having a labeling substance incorporated into its structure because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance to a linker for a scFv;

The specific positions and/or regions of the linker sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices of linkers much less labeling substances is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed labeled single chain antibody in a manner reasonably correlated with the scope of the claims broadly including any scFv linker capable of binding to a labeling substance or having a labeling substance incorporated into its structure. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the single chain antibody structure and still maintain antigen binding activity and labeling substance activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: Modifications to the linker of the scFv are unpredictable in their effects on binding activity

The single chain antibody (scFv) typically comprises a single peptide with the sequence VH-linker-VL or VL-linker-VH. The linker is chosen to permit the heavy chain and light chain to bind together in their proper conformational orientation (see for example, Huston et al., 1991, Methods in Enzym. 203:46-88). "The linker can span the distance between its points of fusion to each of the variable domains (e.g., 3.5 nm) to minimize distortion of the native Fv conformation, and the linker is hydrophilic and sufficiently flexible such that the VH and VL domains can adopt the conformation necessary to detect antigen (US 20060115485; published June 1, 2006; at [0443]). And WO 95/04069 (published 2/9/05; cited in the IDS of 1/18/05) defines a linker as "a molecule that connects two molecules and often serves to place the two molecules in a preferred configuration, e.g., so that a ligand can bind to a receptor with minimal steric hindrance" (p. 8, lines 21-25). Thus none of the art references so much as suggest that any modification can be made to just any linker without having to consider the effects of the modification on the overall structure and function of the scfv molecule. A labeled

single chain antibody would not have an apparent use under 112, first paragraph for the claims scope, if the labeling substance either in being bound to the linker or being incorporated into the linker, prevented the antibody from binding to its cognate antigen, but which otherwise was detectable through the label. Similarly, if the label was not detectable but the antibody portion retained its binding function, the labeled single chain antibody would not have an apparent use under 112, first paragraph for the claims scope.

The specification and the prior art provide insufficient direction and guidance regarding how to produce the genus of labeled single chain antibodies comprising the genus of linkers as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Unpredictability/ undue experimentation

The artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate linkers and labeling substances that could bind to or be incorporated into the linker region, perform the molecular biology to generate a scfv comprising the modified linker, produce and express the modified scfvs, measure binding characteristics for the antibody portion and the labeling substance portion of the scfv (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody), and then finally perform bioassays to identify any one or more of the characteristics of a labeled scfv antibody. The technology to perform

these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single linker-modified scfv antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one linker encompassed by the claims would result in *just any* labeled scfv antibody clone having retained the antigen binding activity and labeling substance activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Partial Signatory Authority